Current Biology
Review

The Neurobiology of Mammalian Navigation

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https://doi.org/10.1016/j.cub.2018.05.050

Mammals have evolved specialized brain systems to support efficient navigation within diverse habitats and over varied distances, but while navigational strategies and sensory mechanisms vary across species, core spatial components appear to be widely shared. This review presents common elements found in mammalian spatial mapping systems, focusing on the cells in the hippocampal formation representing orientational and locational spatial information, and 'core' mammalian hippocampal circuitry. Mammalian spatial mapping systems make use of both *allothetic* cues (space-defining cues in the external environment) and *idiothetic* cues (cues derived from self-motion). As examples of each cue type, we discuss: environmental boundaries, which control both orientational and locational neuronal activity and behaviour; and 'path integration', a process that allows the estimation of linear translation from velocity signals, thought to depend upon grid cells in the entorhinal cortex. Building cognitive maps entails sampling environments: we consider how the mapping system controls exploration to acquire spatial information, and how exploratory strategies may integrate idiothetic with allothetic information. We discuss how 'replay' may act to consolidate spatial maps, and simulate trajectories to aid navigational planning. Finally, we discuss grid cell models of vector navigation.

Introduction

Any mobile organism can gain an adaptive advantage by moving about its environment in such a way as to optimise its chances of survival and reproduction, for example finding food, and avoiding predation. There is a natural dynamic tension between the need to explore (in order to locate new resources) and the need to exploit existing discoveries [1]. For example, as resources are used up at one location, it becomes favourable to move to a new and previously unexplored one. In many species this entails storing information about the environment. In mammals, specialised brain systems appear to have evolved to support efficient purposeful navigation. The neurobiology of mammalian navigation accommodates the huge variety of habitats mammals occupy, from dense forest to desert, from open skies to oceans, and the substantial ranges over which many species forage, explore and migrate. This allows some species to return to a home base having travelled hundreds of kilometres [2–4]. While such naturalistic observations offer some sense of the sheer scope of mammalian navigation and insight into behaviours guided by evolutionary principles, laboratory studies allow for better control of environmental variables and investigation into underlying brain systems. Drawing on such studies below, we first outline the building blocks of navigation: spatial neurons in the *hippocampal formation* (see Box 1 for a glossary of key terms used in this review, highlighted on first use in the text by italics), and the hippocampal anatomical circuitry supporting spatial mapping. We then go on to consider some ideas of how spatial maps are built, supported by hippocampus-directed exploratory behaviour, consolidated, and retrieved in the service of navigation and spatial planning.

Navigation in the Laboratory

Early laboratory studies in rats demonstrated that significant learning could occur during exploration without explicit reward [5,6], and that goal-directed actions, reflecting acquired spatial knowledge, could be employed without having ever been practiced (for example [7]). These studies led Tolman [6] to the belief that something akin to a 'field map' of the environment becomes established in the rat's brain during learning, allowing for more flexible cognitive functions, such as the ability to generate novel shortcuts when familiar routes are unavailable [6,8,9] (but also see [10]). Tolman's *cognitive map* theory was greatly refined and extended after the discovery of putative neural correlates of a map-like representation, namely place cells (described below), found in the hippocampus [11].

Spatial learning of this sort contrasted with reinforcement-based learning, in that it allowed for the acquisition of new spatial knowledge in the absence of either reward or competition between cues for learning, phenomena that traditional associative models of learning struggle to account for [12] (also see [13] for a review). It later became clear, however, that in many situations spatial behaviour could be supported by both latent learning and reinforcement-based mechanisms. Tasks that demanded goal-directed navigation and flexible planning would depend on the hippocampus, while more routine spatial behaviours, such as following familiar routes might rely on stimulus–response associations — for example, at a junction (stimulus), turn left (response) — implemented by separate brain systems whose contributions could be dissociated, for example, by inactivation [14]. An important theme of research in this area has thus been to develop tasks capable of isolating flexible 'map'-based navigation strategies from spatial routines.

Below, in our consideration of the mechanisms of navigation, we discuss results from several tasks in the laboratory, including random foraging, used to investigate spatial representation and learning and its neurobiology (see [15] for a recent review): however, the most widely used behavioural assay of navigation is the watermaze task [16]. Rodents learn to escape from a tank of

Box 1. Glossary of terms.

Allocentric
An allocentric reference frame is one which defines space relative to the external world. This contrasts with an egocentric reference frame, which defines space relative to the body.

Allothetic cues
Space-defining cues in the environment external to the animal, such as the sun, a tree, a river.

Boundary cell, boundary vector cell, border cell
The firing of a 'boundary cell' is primarily determined by environmental boundaries such as vertical surfaces ('walls') or drop edges ('cliffs'). The term 'boundary cell' includes boundary vector cells and border cells. A boundary vector cell fires at a preferred distance and direction from an environmental boundary, for example whenever there is a boundary 40 cm to the north of the animal. A border cell is defined simply by the characteristic that most of its locational firing field occurs adjacent to a boundary. Boundary vector cells and border cells were first reported using different terminologies in the subiculum (2006) and medial entorhinal cortex (2008), respectively; their spatial characteristics likely greatly overlap.

Cognitive map
A cognitive map is a neural model of the external spatial world which represents the distances and directions between places. It enables generation of paths, such as detours or shortcuts, never previously taken, and planning pertaining to currently imperceptible places. Several forms of localisation and navigation do not require information-rich cognitive maps, and the existence of cognitive maps is sometimes questioned.

Grid cell
A grid cell is a neuron that fires whenever the animal is located at one of the vertices of a periodic triangular array tessellating the entire extent of an explored space. Grid cells are thought to provide a coordinate frame to cognitive maps, and to support path integration using self-motion cues, but they are also influenced by allothetic cues such as boundaries. Theoretical models outline how grid cells may be used to compute vectors from a starting point to goal location.

Headscans
Headscans are rodent head movements, especially lateral movements, which enable the animal to sample different views of the environment from a single location. Headscans typically occur during pauses to locomotion, with or without rearing upon hindlegs, and increase upon introduction to novel and altered environments.

Head direction cell
A head direction cell is a neuron that fires whenever the animal's head faces a particular direction relative to the environment. In rodents, a given head direction cell encodes a specific azimuth. In bats, head direction cells are tuned to azimuth, pitch, or roll, or combinations thereof, but most show azimuth tuning.

Hippocampal formation
Typically understood to include the hippocampus proper (the Cornu Ammonis subfields CA1, CA2, and CA3), the dentate gyrus, subiculum, parasubiculum, presubiculum, and medial and lateral entorhinal cortices.

Idiothetic cues
These are cues relating to the animal's self-motion, enabling updating of heading and position. Idiothetic cues support path integration. Although visual and auditory cues are located outside the animal, many researchers consider use of visual and optic flow as idiothetic processing, supporting path integration.

Path integration
Path integration is a self-motion-based estimation of current position and heading, computed by calculating how the subject's own movements have effected spatial translation since last-known position and heading. It is sometimes understood as referring specifically to the calculations supporting return to a starting location.

Place cell
A place cell is a hippocampal pyramidal neuron that fires in one or more restricted regions of space. An individual place cell fires differently, often unpredictably, in different spatial contexts ('remapping').

Rearing
Rearing on hind legs is an exploratory behaviour shown by many four-legged mammals, including rodents, dogs and primates, by which the animal raises its head high, presumably to sample more distal cues, such as visual or olfactory cues, than those available at lower levels.

Ring attractor
A ring attractor is a type of neural network architecture widely hypothesised to support head direction signalling whereby head direction cells with similar preferred directions excite each other, but cells with different preferred directions inhibit each other.

(Continued on next page)

Box 1. *Continued*

Speed cell
A speed cell is a neuron whose firing rate is robustly correlated, typically positively and linearly, with the running speed of the animal. Speed cells are thought to provide input to grid cells to support path integration.

Theta phase precession
A temporal coding phenomenon, observed first in place cells in 1993 and then also in grid cells, whereby a given cell's action potentials (spikes) occur at progressively earlier phases of the local theta oscillation as the animal traverses the spatial field. The precise mechanisms underlying phase precession remain unclear. Phase precession may contribute to coding 'distance-through-field' and spatial sequences.

Theta sweep
A theta sweep is a non-local coding phenomenon occurring during the theta oscillation, whereby hippocampal place cells transiently encode a sequence of locations resembling potential future paths, for example when an animal is at a choice point in a maze. It is thought to serve a 'lookahead' function (for example 'What is at end of west and east arms?') contributing to decision-making (for example 'Ah, I should turn left'). Theta sweeps and theta phase precession may share some underlying mechanisms.

Time cell
A time cell is a hippocampal neuron that fires at a specific stage of a temporal sequence. Different time cells fire at different stages of the sequence (for example the initial, middle or last few seconds of a minute-long epoch) and with varying durations.

opaque water by swimming to a small hidden platform beneath the water surface. Crucially, the platform cannot be identified by local olfactory, visual or auditory cues, and can only be identified by tactile cues when the animal bumps into it. Accordingly, the animal first typically swims quasi-randomly until it happens upon the hidden platform, then gradually learns to use available visual cues and its self-motion to navigate to the platform location. Navigational accuracy typically improves quickly. The watermaze, while specifically designed to test 'cognitive map' theory [11], can examine various types of navigation. Thus, rats can find the hidden platform by using an array of distal visual cues [16], a beacon [17], a landmark at a defined vector from the goal [18], or the geometric arrangement of pool walls [19] or of proximal landmarks [20]. The discovery that damage to the hippocampus of the rat brain greatly impairs navigation relying on a map-like representation of distal landmarks [16] provided further support for O'Keefe and Nadel's [11] theory.

Spatial Cells within the Hippocampal Formation

The bedrock of O'Keefe and Nadel's [11] theory was the discovery of individual neurons, or *place cells*, in the rat hippocampus that only fired when the animal entered a specific location within its environment, the neuron's 'place field' (Figure 1A,B). A given place cell shows different place fields in different environments (Figure 1I,J) or fires in one environment and not the other ('remapping' [21–25]). Different place cells have different fields within the same environment. In open fields, place-field firing rates are generally invariant to the animal's orientation and travel direction [26], but on linear tracks, fields are largely unidirectional. Place cells have more place fields in larger environments [27], but, unlike those of grid cells (discussed below), these fields are not periodic. Several other cellular building blocks of the 'cognitive map', reviewed by [21,23,24,28], have been found in the *hippocampal formation*; these cell types are briefly described below.

Boundary cells, including *boundary vector cells* and *border cells* [29–33], fire whenever a boundary is encountered at a specific distance and direction from the navigator (Figure 1C and Figure 2), with each boundary cell having a different preferred distance/direction. Boundary cells respond to boundaries with different sensory properties [32,33]; potentially, a tree trunk, rock face, cliff edge or even a patch of mud can all serve as boundary cues (Figure 1C).

G*rid cells* [34] are thought to provide the map with a coordinate frame. In well-explored open spaces, a grid cell has multiple firing fields (nodes) which tessellate the environment with a regular triangular pattern (Figure 1D), whereby each node is surrounded by six nodes creating a hexagon. In restricted environments such as hairpin mazes, this triangular pattern is not observed [35]. Grid cell organization in the medial entorhinal cortex is modular [36,37]: for instance, grid scale — node diameter and inter-node distance, both closely correlated — differs for different modules, progressively increasing in quantal steps (~1.5x steps) along the dorsoventral axis of the medial entorhinal cortex, but is very similar for grid cells within a module. How grids are formed is intensely researched and debated, but the consensus view is they support *path integration* (reviewed [38–41]).

Head direction cells [28] provide the navigating animal with a compass-like sense of direction. In rodents, a given head direction cell encodes a specific direction (azimuth) relative to the environment (Figure 1G), independently of the animal's location [28], with different head direction cells having different preferred directions. In bats, head direction cells are tuned to azimuth, pitch or roll, or combinations thereof, but most show azimuth tuning [42]. Head orientation in rodents appears largely based not on magnetic inputs, but on external cues and self-motion cues generated by head rotations. Orientation is crucial for a functional spatial network; the orientation of all other spatial cells (including place, boundary and grid cells) depends on head direction orientation [28,43], and the head direction cell signal,

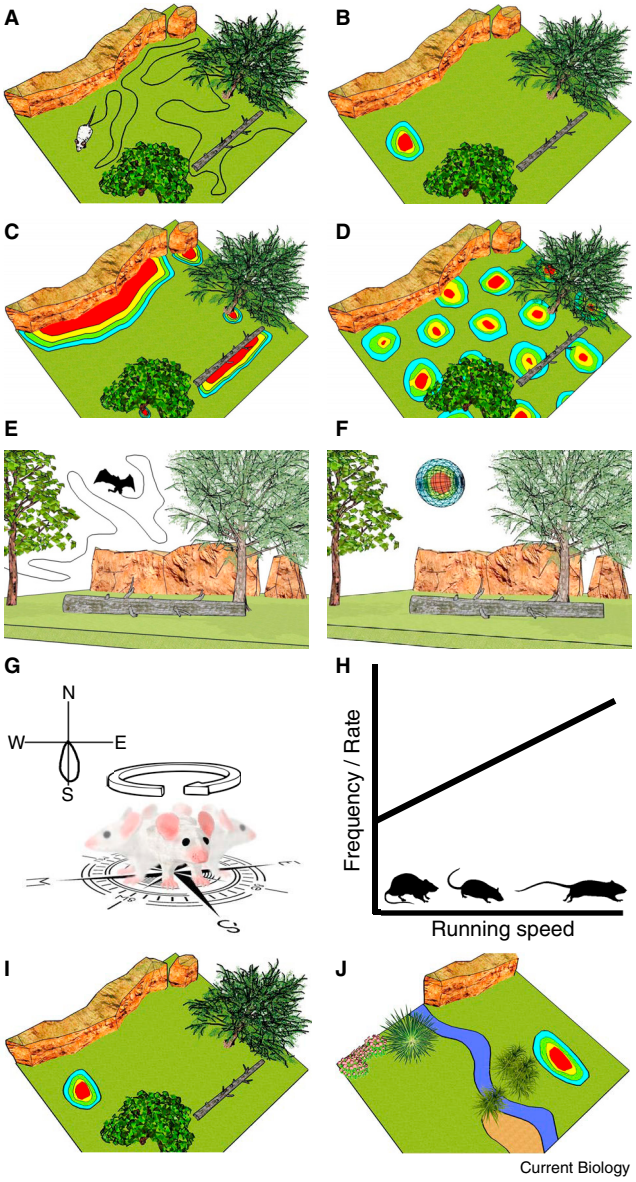

Figure 1. Schematic illustration of different types of spatial cell in the hippocampal formation.

Experimenters typically record spatial cells from an animal while it continuously forages in a confined two-dimensional space (A) or three-dimensional space (E). Schematic examples of firing rate maps for a place cell (B), boundary vector cell (C), and grid cell (D), as recorded from a rodent, and place cell with spherical place field (F), as recorded from a bat [207]. Red portion of firing field denotes region of highest firing, yellow portion region of second-highest firing, and so on. (G) An example rodent head direction cell, which fires strongly when the animal faces cell's preferred direction, here southwards. (H) A typical linear increase in frequency of an oscillation (such as hippocampal theta [52]) or in the firing rate of a speed cell [49,50] as an animal increases running speed. Which type of speed-related signal contributes to generating grid cell signals is debated. (I,J) Place cell 'remapping' [25], whereby the same place cell exhibits different, non-corresponding place fields in different environments. Less-well characterised spatial cells not illustrated here include landmark vector cells in the hippocampus [97] and axis-of-travel cells in the subiculum [202].

likely supported by a *ring attractor* network, comes online in development before other spatial cells [44–47].

Though these spatial cells have mainly been studied in ground-dwelling rodents (with spatial fields normally identified in two dimensions) there is evidence from flying bats [21], as well as rodents and humans exploring complex structures [48], that the building blocks of the cognitive map can also represent three-dimensional space (Figure 1E,F). And beyond abstract spatial parameters, cells within the hippocampal formation also encode self-motion information more directly. Notably, *speed cells* increase their firing rates as running speed increases (Figure 1H), enabling calculation of how far the animal has travelled [49,50].

Self-motion is also linked to another prominent feature of the electrophysiology of the hippocampal formation: the theta oscillation (4–12 Hz) which is seen in local field potentials during locomotion in rodents and primates (including humans [51]). Theta appears to be closely linked to the spatial functions of the hippocampal formation. The frequency (and power) of theta correlates positively with running speed (Figure 1H) [52], and robust speed–frequency relationships likely enable *theta phase precession*, whereby spikes occur at progressively earlier phases of the theta oscillation as the animal traverses the place field (Figure 3A–C). Phase precession, shown by place cells [53] and grid cells [34], implies theta phase coding of distance-through-firing-field, and is very obvious in linear tracks [53,54], but also occurs in two-dimensional environments [55,56].

Importantly, theta phase coding of distance-through-field observed in place cells and grid cells is cell-specific, contributing to 'theta sequences' [54,57,58] (Figure 3D–F), whereby the spatial sequences encountered on environmental routes are, in effect, converted into temporal sequences clocked by theta. Place cells firing at later, intermediate, and early theta phases will have their firing field peaks ahead of, at, and behind the animal's current location, respectively; thus, the spatial sequence of place fields on the track (red-to-green-to-blue, Figure 3D) is present in the temporal order of firing within each cycle (red-then-green-then-blue, Figure 3F) [54,59]. This aids sequence coding, likely contributing to mechanisms in *theta sweeps* where the animal shows 'lookahead' place-field sequences corresponding to future path segments [58,60]. Implications of theta phase precession for consolidation and navigational planning are considered later in this review.

Alongside studies in rodents, studies with human participants are particularly useful in placing cellular results in a wider context. Humans are able to follow complex task instructions and — often using multivoxel decoding techniques in conjunction with virtual environments — brain mechanisms of navigation can be investigated by functional magnetic resonance imaging (fMRI; for review see [61]). These studies suggest that the hippocampal spatial coding system observed in animals is essentially preserved in humans. For example, signals of location or episodic spatial context [62,63] were detected within the hippocampal formation [64], while hexa-directional responses consistent with a grid-cell-like representation have been found in human entorhinal cortex [65,66] (and also in monkey entorhinal cortex [67]). Crucially, these macroscopic observations from fMRI are supported by rarer electrophysiological studies in patients implanted with electrodes. These have identified neurons

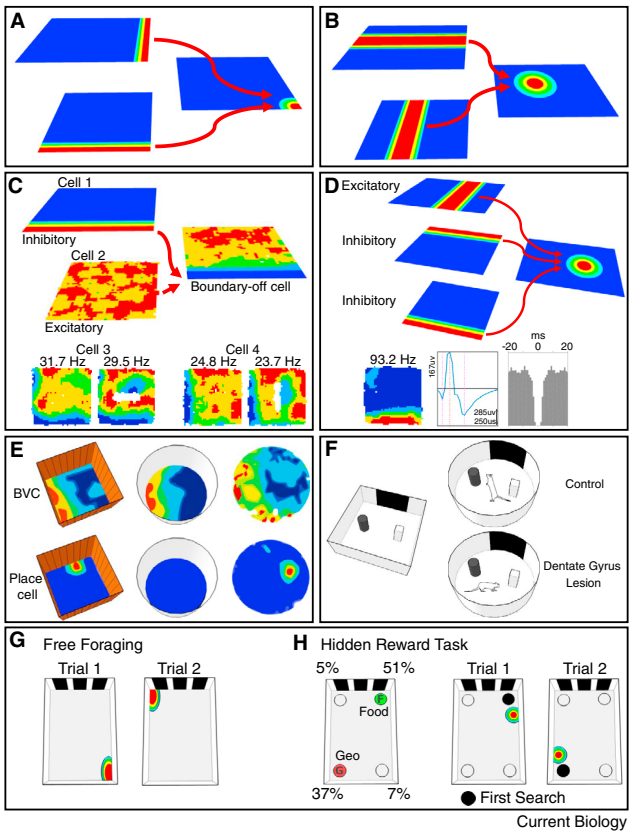

Figure 2. Influence of environmental boundaries upon spatial coding and behaviour.

Schematic illustration of the original boundary vector cell model [102] of inputs to place cells (A,B) and potential extensions to the model (C,D). (A) A place cell's place field in the south-east corner of square-walled box is formed from thresholded summation of inputs from BVCs with firing fields along east and south wall. (B) Similarly, a place field in the north-west central region formed from boundary vector cells with fields somewhat distal to north and distal to west walls. (C) A boundary-off cell which shows reduced firing along the south wall (top-right map) can be modelled [33] as combining excitatory input from all regions within an environment (cell 2), with input from an inhibitory boundary vector cell firing along south wall (cell 1). Bottom row depicts firing rate maps from two real subicular boundary-off cells (cells 3 and 4) before (left) and after (right) insertion of a walled barrier in the centre of the environment. Note the barrier induces an additional zone of reduced firing (blue portions) in expected location. Values in Hz indicate peak firing rate after smoothing. (E) Geometry-specific, feature-insensitive boundary firing: top row, broadly similar firing of a boundary vector cell in three different environments, largely insensitive to changes in sensory features and spatial context; bottom row, a place cell remaps in each environment. (Schematic illustration based on [32].) (F) Lesions to dentate gyrus prevent increases in exploratory behaviour (rearing on hind legs) elicited by changes to geometry of environmental boundaries. Rats trained repeatedly in a square-shaped enclosure (left) are exposed in a test trial to a new cylinder-shaped enclosure (right), while between-object distance and cue-card orientation are preserved. Control rats increase rearing frequency in new shape, but rats with dentate gyrus lesions do not. Schematic illustration based on [140]. (G,H) Schematic diagram demonstrating the results of Keinath *et al.* [154]. In both experiments described, mice were disoriented, via passive rotation, before exploring a rectangular box, during which hippocampal place cell activity was recorded. In the first experiment (G), mice randomly foraged for food throughout the environment. To establish heading, the only cues available were the local geometry provided by the walls of the box and the polarising black and white wall. As illustrated by the activity of a single place cell in this example, the place fields were anchored to the local geometry (note the rotation to a geometrically equivalent but visually distinct location between trials 1 and 2). In a second experiment (H), mice were required to find food in one corner of the box. The first search distribution (left-hand image) revealed that reorientation was guided primarily by the geometry of the walls: the mice first searched in the food corner (green circle) or, equally as often, in the geometric equivalent corner (red circle), while apparently ignoring the disambiguating visual cue (striped wall). The orientation of the recovered place cell representation was highly correlated with the corner in which the mice first searched for food and could reliably predict the to-be-searched corner on each trial. Trials 1 and 2 offer an example: when the place field is located close to the north-east corner during trial 1, the mouse first searches for food (depicted by a black circle) in the north-east corner. However, when the place field rotates 180° to a geometrically equivalent location in trial 2, the mouse's first search behaviour (black circle) exhibits the same rotational shift.

that correspond to place [68,69] and grid cells [70], with some evidence of head-direction-like responses from 'path cells' [71], while new evidence from intracranial theta recordings indicates that human subiculum may code for goal locations relative to environmental boundaries [72].

The greater coverage of fMRI (as compared with electrophysiological methods) has revealed the coding of spatial variables within a wider navigation network, including retrosplenial cortex, parahippocampal cortex, and superior-lateral occipital cortex. Notably, location-related and heading-related signals can be decoded in retrosplenial cortex [63,73], with head-direction-like responses observed in the thalamus [74]. There are also signs that the posterior cortical regions are sensitive to aspects of environmental scale, boundaries and barriers to movement [75–78]. Establishing the precise form these representations take and the complementary roles of distinct regions remains a topic of current research. It is clear, however, that the human navigation network overlaps substantially with regions involved in visual scene processing [79] and with the 'default mode network' [80], suggesting that these regions participate in the extraction of such spatial information from visual scenes and in the construction of spatial imagery during spontaneous thought, memory retrieval and planning [81,82].

While these studies suggest substantial cross-species continuity in spatial representation and processing, and potentially extend our understanding of links between navigation and other forms of cognition, rather basic questions about information flow remain. For instance: what are the key inputs to place cells? What is the relationship between different spatial cell types? To help answer these questions, we introduce the anatomy of the hippocampal formation.

Functional Anatomy of the Hippocampal Formation

Neuroanatomical Overview

A rodent-based functional anatomy of the hippocampal formation in Box 2 outlines the core mammalian wiring diagram, two axes of organisation (a long axis and a proximo-distal axis) and navigation-related functions associated with two features: the CA3 collaterals and the dentate gyrus. Here, we discuss information flow in this network, focusing on place cells, grid cells, and boundary cells, grounded upon entorhinal-hippocampal and subiculum-hippocampal projections.

Place cells are found in the dentate gyrus and hippocampus proper. The head direction signal is built up subcortically and mainly conveyed to the hippocampus from anterior thalamus via the parasubiculum, presubiculum and entorhinal cortex [28]. What about locational inputs to the hippocampus? A long-hypothesised input to place cells is provided by boundary cells, found in input and output regions of the hippocampal

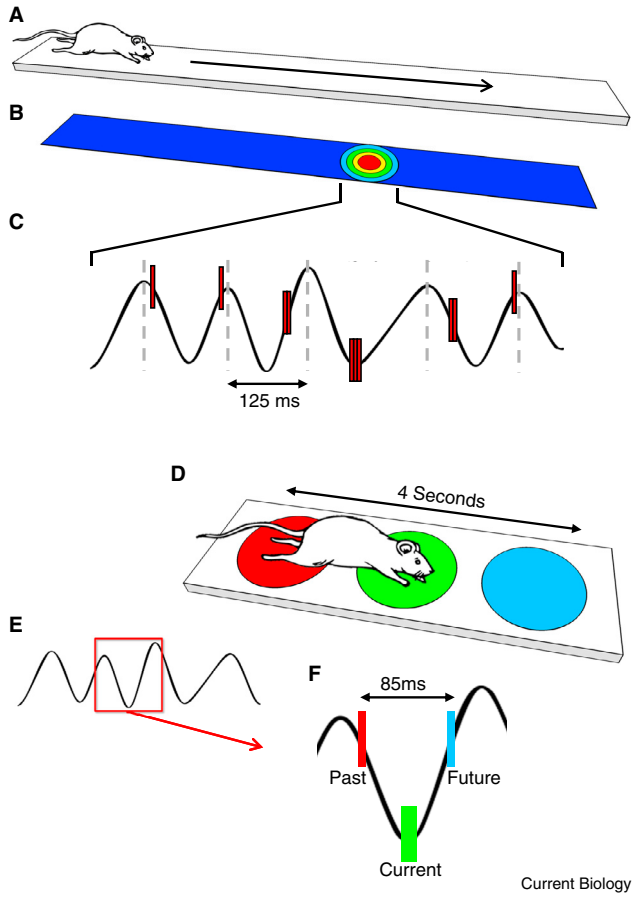

Figure 3. Idealised examples of theta phase precession and a 'theta sequence'.
(A–C) Theta phase precession of place cell firing. (A) As a rat runs along a linear track, a hippocampal place cell fires (B) as the rat moves through the cell's place field. (C) The firing rate code for location is also a temporal code: spikes (vertical red bars) fire at successively earlier phases of the theta oscillation (black sinusoidal trace) — theta phase precession. (D–F) A 'theta sequence' emerges from theta phase precession of different place cells, in which a spatial sequence is represented temporally within a theta cycle. (D) Rat runs through different place fields in a fixed sequence ('red to green to blue'). (E, F) Within a single theta cycle (red square is ~1.2 cycles), place cells firing at later (blue), intermediate (green), and early (red) theta phases will have their firing field peaks ahead of (blue), at (green), and behind (red) the animal's current location, respectively. In effect, theta sequences compress spatial sequences, perhaps enabling consolidation of spatial routes via spike-timing-dependent plasticity.

formation including the subiculum [29,32,33], and both input (superficial) layers and output (deep) layers of the medial entorhinal cortex [30,31,83], presubiculum and parasubiculum [84]. Grid cells are presumed to provide major inputs to place cells, but they are found throughout hippocampal-receiving, as well as hippocampus-projecting, regions of the medial entorhinal cortex, presubiculum, and parasubiculum [34,36,84]. As boundary and grid cells are found in both hippocampal input and output regions, understanding their particular contributions is proving challenging.

Entorhinal-Hippocampal Projections and Grid Cells

Grid cells are most numerous, and their firing fields most grid-like, in the medial entorhinal cortex [84,85], so understanding the role of this entorhinal input to place cell function is a key issue. Interactions between entorhinal cells and hippocampal place cells, including the relative importance of the direct versus indirect entorhinal-to-CA field projections (Figure 4A), are not fully understood. Basic place-cell characteristics are preserved in CA1 when all CA3–CA1 input is removed, though behavioural recall in the watermaze task is impaired [86]. Lesioning entorhinal layer 3, which removes the entorhinal–CA1 field and entorhinal–subiculum projections, impairs spatial precision of CA1 cells but not of CA3 cells, which receive input from entorhinal layer 2 [87]. Larger lesions of medial entorhinal cortex only partially disrupt locational signals in place cells, but strongly affect their temporal firing (notably theta phase precession) [88–90] and impair water-maze navigation.

Several studies suggest that the locational responses of place cells can arise independently of grid cell input [45,47,91,92]. Indeed, it is currently easier to argue that hippocampal output, potentially including CA1 place cells and subicular boundary cells [32], seems crucial to grid cells [93–95], than the opposite. Taken together, the studies cited in this section suggest that the hippocampal formation supports navigation, that entorhinal input is important to place cells, but that place-cell locational signals come from multiple sources, not just grid cells. As such, it is important to consider other sources, including cues from boundaries [29–32,96] and landmarks and objects [97,98]. More is known about boundary cells and we focus on those here. Consistent with being important input to place cells and grid cells, both entorhinal- and subicular boundary cells appear early in development [83,99].

The Boundary Cell Network

While early place cell research emphasized place cell 'remapping' following changes in gross environmental features, later studies that manipulated environmental geometry alone demonstrated that place cells typically fired in corresponding locations in geometrically different environments, specifically in locations that tended to maintain their distance to the nearer walls of each environment [100,101]. This led to the boundary vector cell model [29,102–104], which explains place fields in terms of geometry-sensitive inputs to the hippocampus. These boundary vector cells were predicted to have firing rates representing preferred distances to environmental boundaries in specific allocentric directions (controlled by the head direction system; Figure 1C and Figure 2A–D). Thus, one boundary vector cell might fire whenever a boundary is perceived ~40 cm to the north of an animal, and this might occur in several regions in a defined space (Figure 1C). Place field(s) could be modelled as the thresholded sum of a few putative boundary vector cells (Figure 2A,B), capturing place cell findings under various geometric manipulations [102]. The subsequent discovery of boundary cells [29–33,96] whose firing fields strongly resembled those of the modelled hippocampal inputs lent support to the boundary vector cell model.

In order to explain place fields located interiorly within an environment, however, the boundary vector cell model assumed that boundary vector cells exhibit a wide range of distance tunings; some argued that the entorhinal cortex (the main input to the hippocampus) contains only border cells with fields adjacent to environmental walls [31,83], and therefore that boundary cells function not to provide inputs to place cells, but rather to anchor grid cells [31,83]. This grid-anchoring idea is certainly

Box 2. Functional anatomy of the hippocampal formation.

Anatomical axes

Two anatomical axes in the hippocampal formation have functional consequences for navigation: the long axis and the 'proximo-distal axis'. The best-characterised of these is the long axis (Figure 4B; reviewed in [208]), which is oriented septal-to-temporal in rodents and posterior-to-anterior in primates (so that the rodent septal pole is equivalent to the primate posterior pole). The septal(rodent)/posterior(primate) pole has been theorised to support spatial cognition and memory, and the temporal(rodent)/anterior(primate) pole anxiety, consistent with rodent [209] and human data [204,210]. Strong two-pole functional dualism seems incompatible with hippocampal physiology, because hippocampal theta appears crucial for spatial, mnemonic and anxiety-related functions [11,38,120], and resembles a single travelling wave along the entire long axis (reviewed in [120]).

The second, 'proximo-distal' axis (reviewed in [211]), illustrated here with reference to CA1 (Figure 4C), is associated with differential contributions of, on the one hand, the medial entorhinal cortex and its major input the postrhinal (aka parahippocampal) cortex, and on the other, the lateral entorhinal cortex and its major input the perirhinal cortex. The lateral entorhinal cortex, typically associated with non-spatial item memory ('WHAT'), targets distal CA1, while medial entorhinal cortex, typically associated with space/navigation ('WHERE'), preferentially targets proximal CA1.

Importantly, Knierim *et al.* [211] argue that *both streams* provide spatial information, with the lateral entorhinal-associated stream providing content-oriented object and location information based on external sensory cues (allothetic), and the medial entorhinal-associated stream providing context-oriented spatial information provided by internal sensory self-motion cues (idiothetic), but also by allothetic cues. Notably, theta-associated idiothetic information, largely absent from lateral entorhinal cortical cells, is strongly present in medial entorhinal cortex, as suggested by the presence of grid cells, speed cells and head direction cells (which while fixing to environmental cues are also strongly controlled by lateral head motion).

CA3 collaterals and the dentate gyrus

The extensive recurrent connections between CA3 pyramidal cells are theorised to support an auto-associative memory [212–214]. By exploiting Hebbian learning in recurrent connections, autoassociative memory allows retrieval of an entire stored representation based on fragments of the original set of cues ('pattern completion'), thus enabling recall, not just recognition. Hippocampal pattern completion via fast and slow attractor dynamics, and CA3's long-hypothesised role in such completion, has now been demonstrated in place cell representations and navigation tasks [45,215–218]. Notably, CA3 plasticity promotes navigating to the watermaze's hidden platform using extramaze cues when most of the previously-presented extramaze cues are removed [216]. This illustrates how pattern completion can be crucial to navigation, since various scene-changing factors (for example daylight, snowfall, decay, seasons) mean environmental cues are seldom exactly as previously encountered (a complementary way of addressing this problem is to store geometric representations that are resistant to scene-changing factors, as discussed in main text). Importantly, interference between similar stored representations poses problems in these auto-associative models; performance is improved when non-overlapping representations are stored.

The dentate gyrus, with high cell numbers (>10x more neurons, septally, than both entorhinal cortex and CA3), is proposed to ensure that similar-but-different rhinal cortical inputs to the hippocampus are stored as non-overlapping representations in CA3 ('pattern separation') [213,214,219,220]. Similar-but-different inputs could occur with novel configurations of the same spatial cues. The dentate gyrus is one of few mammalian brain regions where adult neurogenesis occurs, and integrating specifically recently-born cells underlies pattern separation. Thus, when neurogenesis is ablated, behavioural discrimination of highly similar locations/contexts is impaired, while promoting survival of newborn cells, or their relative contribution as input to CA3, improves pattern separation [221,222]. Enabling mapping of new spatial contexts with minimal interference likely partly underlies neurogenesis' importance in hippocampal-dependent spatial tasks, such as classic watermaze navigation [223,224].

reasonable. Boundary representations seem to correct the cumulative error in grid cells' computations of path integration. When an animal spends a long time away from a boundary, grid cell spatiality is disrupted [105]. Moreover, environmental boundaries exert powerful effects upon grid cell organization, including upon 'gridness' (the hexagonality of fields), grid scale and orientation [37,106,107], presumably mediated by boundary cells, whether directly or via place cells [108].

Do boundary cells function as inputs to place cells as well as to grid cells? We previously reported boundary vector cells with firing patterns consistent with longer-range tunings in the subiculum [32]. A reasonable counter-claim, however, is that subiculum is primarily a hippocampal output structure [83,109]. How might this debate be resolved? Three potential resolutions can be suggested. First, distally-tuned boundary cells may be too rare to be important, favouring accounts where the role of boundary cells is confined to grid cell anchoring [31,83]. Second, manipulations in large-scale environments may reveal longer-range distance tuning in boundary cells in classic input regions. And third, complementing the second point, subicular boundary vector cells may provide input to hippocampus proper (Figures 2 and 4).

Importantly, recent evidence shows very substantial direct projections from subiculum to CA1: in fact, the largest cortical input to distal CA1 is from the subiculum (denoted by thickest black line, Figure 4Cix) [110,111]. Moreover, while traditional lamellar slice preparations indicate information flow from CA3 towards CA1 and subiculum, more realistic (larger, longitudinal) slice preparations show theta-related information flow from subiculum towards CA3 and CA1 [112], consistent with subiculum acting as input to hippocampus. Further, consistent with direct subiculum–CA1 projections coming from both subicular

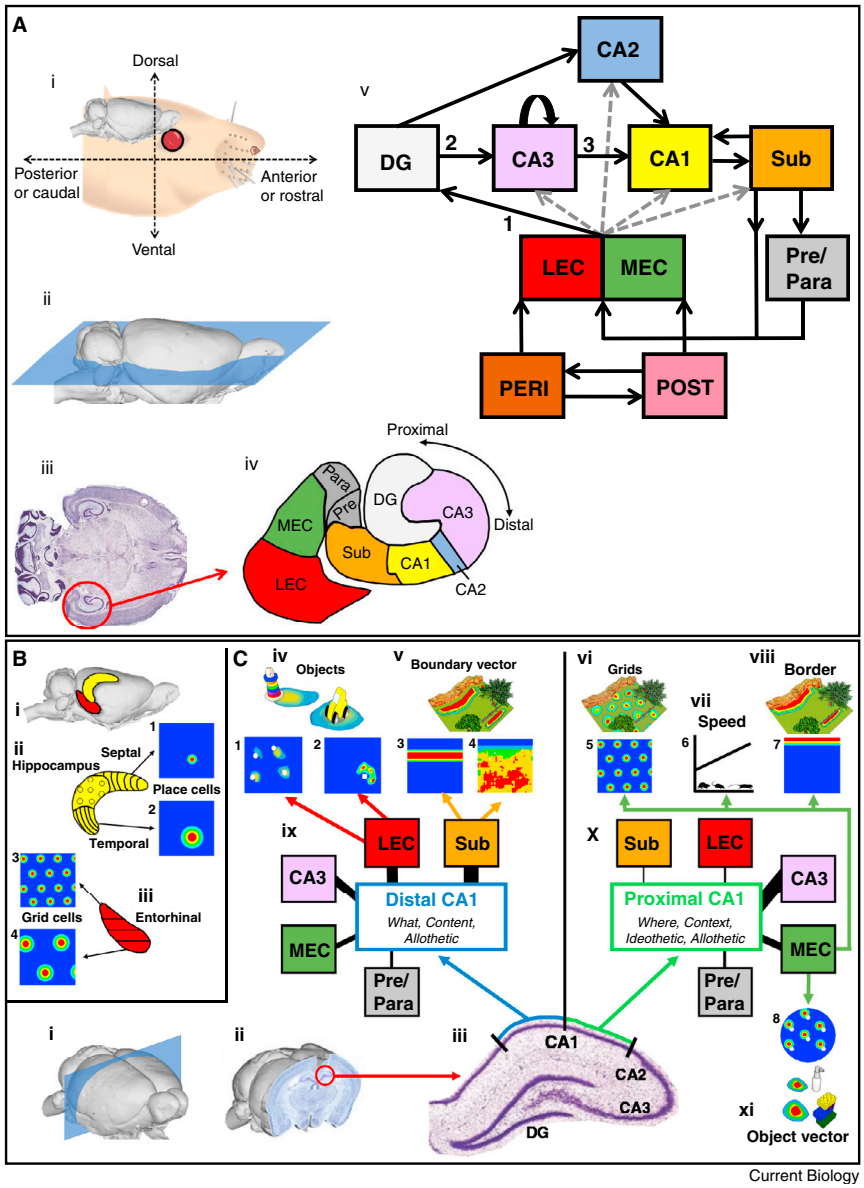

Figure 4. Anatomy of the hippocampal formation.

(A) Overview of connectivity. (Ai) Cartoon of whole rat brain within the head. (Aii) Depiction of 'horizontal' sectioning plane. (Aiii) Horizontal histological section, with hippocampal formation circled in red. (Aiv) Representation of regions within the hippocampal formation, comprising lateral entorhinal cortex (LEC), medial entorhinal cortex (MEC), parasubiculum (Para), presubiculum (Pre), subiculum (Sub), CA1, CA2, CA3, and dentate gyrus (DG). (Av) Overview wiring diagram. Superficial layers of entorhinal cortex, to which the presubiculum and parasubiculum densely project, are mainly input layers, acting as a major conduit for neocortical and subcortical information to reach the hippocampus, while entorhinal deep layers, subiculum, and CA1 provide output from hippocampus to the rest of the brain. Perirhinal cortex (PERI) and postrhinal cortex (POST, homologous to parahippocampal cortex in primates) project preferentially to LEC and MEC, respectively. Anatomical overviews have emphasised the largely unidirectional nature of hippocampal circuitry. The 'trisynaptic circuit' comprises these projections (see numbered arrows in Av): (1) entorhinal cortex to dentate gyrus; (2) dentate gyrus to CA3; (3) CA3 to CA1. The CA1-to-subiculum projection can be considered the 'fourth synapse' extending the trisynaptic circuit. Projections from CA1 and subiculum to the entorhinal cortex close the loop. The 'trisynaptic circuit' overview of hippocampal pathways is incomplete because of substantial direct projections from entorhinal cortex to CA fields and subiculum (dashed grey arrows), substantial longitudinal projections along the hippocampal long-axis, and 'reverse' projections such as from subiculum to CA1 (potentially carrying boundary vector cell signals; see main text). Importantly, CA3 pyramidal neurons make substantial projections to themselves ('recurrent collaterals', semi-circular arrow) as well as to CA1. (B) Hippocampal long axis. (Bi) Whole rat brain showing long axis of the hippocampus (yellow) and entorhinal cortex (red). (Bii) Cartoon of place cells (cell 1, small-scale; 2, large scale). (Biii) Cartoon of grid cells (cell 3, small-scale; cell 4, large scale), with spatial scales smaller at the septal hippocampal and caudomedial entorhinal ends. (C) Proximo-distal axis of CA1. (Ci) Whole rat brain depicting 'coronal' sectioning plane. (Cii) Coronal histological section with hippocampus circled in red. (Ciii) Coronal hippocampal section showing distal (blue) and proximal (green) ends of CA1). (Civ,Cv) Spatial input to distal CA1 includes the following cell types (numbered): (1) and (2) object-related spatial cells [97,225] both in lateral entorhinal cortex; (3) boundary vector cell and (4) boundary-off cell, both in subiculum. (Cvi, Cvii, Cviii, Cxi) Spatial input to proximal CA1 includes the following cell types: (5) grid cell; (6) speed cell; (7) border cell; (8) object vector cell [98], all found in medial entorhinal cortex. The strongest hippocampal formation inputs to distal CA1 come from subiculum and lateral entorhinal cortex (Cix); in turn, these regions provide the weakest inputs to proximal CA1, where instead CA3 and medial entorhinal cortex input dominate (Cx) [111]. Thickness of arrows denotes strength of projection, normalised to strongest input (subiculum strongest for distal CA1, CA3 strongest for proximal CA1), based on [111].

excitatory pyramidal cells and inhibitory interneurons [110], we hypothesise subiculum-to-CA field information flow includes boundary vector input that is inhibitory as well as excitatory. In short, it remains very possible that boundary cells provide a functionally significant input to hippocampal place cells as predicted by the boundary vector cell model.

Boundaries and Inhibition

Why do we suggest inhibitory boundary vector input? Boundary cells include 'boundary-off cells' (Figure 2C) [33]. Appearing like short-range 'inverse' boundary vector cells, a boundary-off cell can simply be modelled as a cell that fires everywhere except in restricted region(s) of inhibition driven by afferent inhibitory boundary vector cells (Figure 2C). This theoretical prediction of boundary vector cell interneurons has yet to be robustly tested, though we have preliminary evidence for such a cell type (Figure 2C) [33]. What function(s) could inhibitory boundary signals serve? One may be that, extending the boundary vector cell model, inhibition also shapes the place field summation process (Figure 2D). Another possibility is that inhibitory boundary vector cells may contribute to grid cell generation. In one speculative model, grid cells are formed from inputs involving interactions between place cells and boundary cells involving a

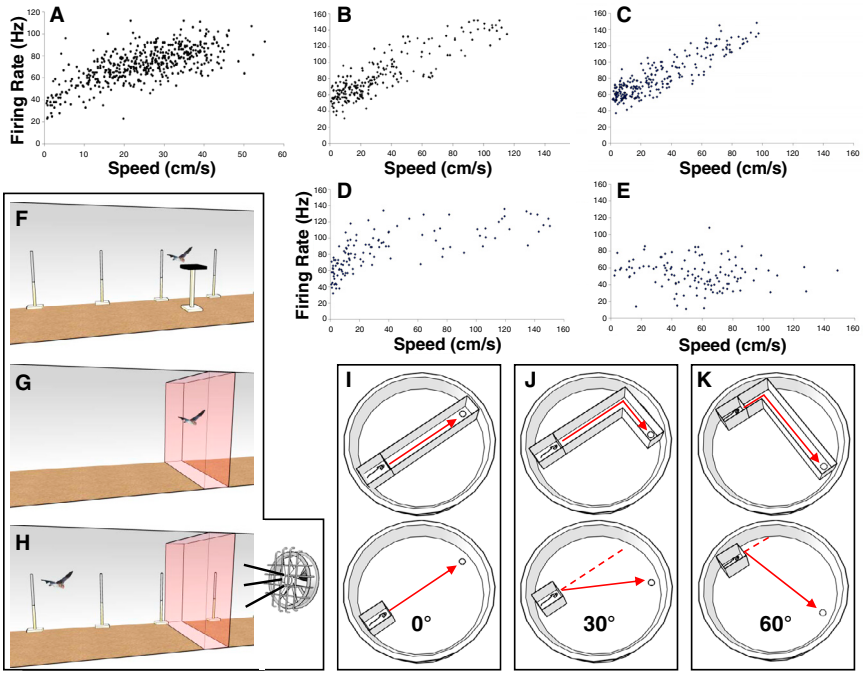

Figure 5. Path integration: sensory contributions to linear displacement and role of grid cells.

Presubiculum speed cell illustrating role of different sensory contributions to speed estimation. Speed cell recorded in a cylinder (A), and then on linear track in light (B) and darkness (C) [50]. Broad similarity of firing-rate-to-speed slopes across light/dark on linear track indicates visual information including optic flow was dispensable for this speed cell (as for the three darkness-tested speed cells in Kropff *et al.* [49]). In contrast, passively displacing the rat in the experimenter's hand greatly changed the rate-to-speed function, which asymptoted at higher speeds (D). This suggests vestibular signals could drive the speed cell, but such signals alone without motor efference and/or proprioception led to errors at higher speeds. Remarkably, passive displacement whilst the rat was restrained in a towel abolished the cell's rate-to-speed function (E). This strongly suggests the importance of a motor efferent signal in this speed cell, though proprioception cannot be ruled out. The insufficiency of the vestibular system alone for accurate updating of linear displacement in this cell (D,E) is consistent with strong disruption to grid cells when rats are passively displaced in carts [226]. Species differences may occur: darkness appears to flatten the slope of the rate-to-speed function in mouse grid cells [115] much more than in rat speed cells [49,50]. (F–H) Path integration task in pipistrelle bats [118]. Bats were trained to collect food from a platform 20 m down a corridor (F) over several weeks. Probe trials, with the feeding platform removed, tested bats' ability to hover at the platform's former location (denoted by pink zone) (G), under various sensory manipulations: wind in (H) for example. Bats used path integration, ignoring acoustic information and landmarks, but used time rather than speed to estimate distance, potentially consistent with 'time cells' in rodents [119]. (I–K) Ablation of NMDA receptors from the retrohippocampal region in mice results in disrupted grid cell firing and a pattern of unimpaired performance in straight-line test trials (I) and watermaze beacon task (not shown), but impaired vector reproduction in the long–short (J) and short–long (K) test trials, showing deficits in simple path integration. Moreover, grid cell disruption correlated with path integration deficits. (Adapted from [125].)

boundary-related repulsive force [94,95]. Many models of navigation require inhibited firing near barriers to select efficient paths, which is particularly important during detour behaviour [33]. Thus, inhibitory boundary vector cells and boundary-off cells may contribute to planning motor sequences that avoid obstacles.

In summary, boundary cells likely provide important allothetic input to place cells and grid cells. Exactly how crucial this input is to place-cell firing is unclear. One potential pointer to boundary cells alone being insufficient for optimal place-cell function is that, in rat pups, place-cell stability is compromised in central regions away from environmental boundaries until the period of grid-cell maturation [113]. This finding suggests a key gain-of-function that grid cells, emerging at weaning, confer upon place cells: grid cells extend the stabilising influence of environmental boundaries far into open space. In the next section, we ask how the mapping systems can utilise self-motion (idiothetic) cues.

Path Integration

How does an animal know how far it has moved? Path integration is the self-motion based estimation of current position and heading, enabled by the animal calculating how its own movements have effected spatial translation since the last-known position and heading. Following the discovery of grid cells, a consensus rapidly emerged around the idea that they provide a critical component of this process, potentially translating sensory information about movement into an index of location [38,39,41,114].

Estimates of linear and angular displacement during locomotion can come from several sources. As the angular contributions are less understood, we focus on linear displacement here. First, motor efference copy, information derived from the collateral discharge of neurons driving movement, for example estimating the vigour and number of strides taken. Second, proprioception, information derived from muscles, joints and tendons, for example estimating stride number and stride extension. Third, vestibular information, capturing acceleration cues from the otoliths and enabling integration of velocity from acceleration, and distance from velocity (information which, importantly, is available during passive translation in the absence of self-generated motion). Fourth, optic flow, information derived from global visual changes during movement, which can be used to derive estimates of linear displacement as well as heading. And fifth, integrating time, assuming a 'standard' travel speed, which could contribute to an estimate of distance.

In Figure 5A–E, rate-to-running-speed relationships in a speed cell are used to illustrate how different sensory modalities contribute to an overall estimate of running speed, and thus potentially of linear displacement. Species differences amongst mammals likely exist. For example darkness may affect speed estimation more in mice than rats [49,50,115,116], and acoustic flow may be more important in some bats than others [117,118]. The findings of Aharon *et al.* [118], partly illustrated here in (Figure 5F–H), suggest that one mammalian strategy to estimate travelled distance is to assume a 'standard' travel speed, and integrate time. This could be aided by *time cells*, which have been

characterised in entorhinal cortex and hippocampus in rodents [119]. A time cell fires at a specific stage of a temporal sequence, with different time cells firing for different durations and at different stages of a sequence, for example the initial, middle or last few seconds of a minute-long epoch. It has been suggested that similar theta-based mechanisms could underlie both grid pattern emergence and time estimation (see [120] for discussion).

Interestingly, GluA1 knockout mice, which show disrupted grid cells and impaired path integration [121], show impaired theta-frequency mechanisms [121] and impaired short-term habituation [122], the latter potentially indicating that time passes more slowly for these mice. We hypothesise that time cells in these mice, while showing the expected stage-in-sequence properties, will exhibit longer firing durations. In summary, different methods for path integration exist, and this is a part of the navigation system that is likely to vary between mammalian species according to the different sensory systems and environmental cues available.

In rodents at least, locomotion velocity is positively correlated with theta frequency (local field potential and cellular interburst frequency) and the firing rates of 'speed cells', as well as that of grid cells and place cells (Figure 1H). A key challenge is to determine how these two candidate velocity signals for estimating linear displacement contribute to path integration. This question relates directly to debates on the mechanisms underlying grid cell generation, with theta frequency mechanisms important under oscillatory interference models, and firing rate important under attractor models; see discussion in [38,39,41,114,123]. It may be fruitful to develop hybrid grid cell models incorporating both oscillatory interference and attractor mechanisms [124].

Importantly, while debates on grid-cell-related mechanisms continue, work linking grid cells to behavioural tests of path integration is now emerging. The importance of grid cell function to path integration is suggested by exciting findings that genetically-induced disruptions to grid cell functionality in mice correlate with deficits in an L-shape path integration task in water (Figure 5I–K) [125] (see also [121]). The mutations do not impair success in a beacon task, suggesting that the deficits are indeed related to path integrative navigation and not more general impairments.

Map-building

The spatial cells of the hippocampal formation provide the building blocks of an allocentric representation that allows a mammal to integrate allothetic information, such as environmental boundary cues, and idiothetic information, such as linear translation cues, to track its current location and relate it to stable and navigationally relevant features of the environment. But in order for this mechanism to be useful, the animal must venture beyond its immediate surroundings to build maps of the wider world.

Environmental Sampling, Novelty Detection, Exploration

Building cognitive maps entails sampling environments. Presumably because the benefits of spatial maps — for example, in reliably predicting the locations of resources, conspecifics and predators — so readily outweigh the costs of their acquisition, the hippocampal formation has evolved to construct and update spatial maps in an ongoing, continuous 'default' fashion. Motivational factors, by affecting synaptic plasticity [126] and boosting 'replay' (discussed below), can further enhance the stability of individual place cell maps and associated memory [127,128]. Such map-building is enhanced when environments are well sampled, for example by revisiting the same location from different directions or sampling different views from the same place.

A central claim of original cognitive map theory was that map building, elicited by novelty detection, is driven by an intrinsic motivation and that, without a hippocampus, animals would lack curiosity and would not exhibit any exploratory activity [11]. Briefly, current evidence supports this view, albeit in a weaker form. While some exploration is clearly hippocampus-independent, spatial-directed exploration is indeed controlled by hippocampus-dependent processes for detecting spatial novelty, which result in increased intrahippocampal neuromodulator levels, in turn enhancing exploration, synaptic plasticity, and eventual storage of new information [120,126,129–133]. Thus, the hippocampus controls overt behaviour in at least two ways: not only in using spatial maps to enable navigation behaviour, but also in directing exploration to enable effective map-building.

Exploration

As well as physically moving about the environment, exploratory behaviours can include actions which enable the animal to gather allothetic information about its current location. In rats, two behaviours, *rearing* on hind legs and *headscans*, are examples. Rearing lifts the head high, presumably to afford better sampling of distal cues (visual or olfactory, for example) than is perceivable at lower levels. Rearing increases in response to spatial (and other) novelty and has been hypothesised to be important in spatial information-gathering [129,134]. Consistent with the neuromodulatory scheme above, cholinergic agonists injected into the medial septum or hippocampus increase rearing, and on first exposure to a novel environment, rearing frequency is highly positively correlated with hippocampal acetylcholine [129].

Various findings [135,136] support the prediction of [129] that rearing, conferring higher viewpoints, is preferentially elicited by distant rather than nearby allothetic cues. This idea has particular relevance for spatial mapping because distal rather than proximal cues tend to dominate the angular orientation of hippocampal spatial maps [28,129,137–139]. Sampling distal cues from multiple viewpoints, rearing is especially suitable for incorporating allothetic cue information regarding location and angular heading into hippocampal spatial representations. Accordingly, when rearing frequency increases because of spatial novelty, rather than anxiety, this increase is hippocampus-dependent [107,114,115]. Moreover, a hippocampal theta frequency variable, the frequency-to-running-speed slope, theoretically associated with spatial-context novelty, consistently predicts rearing frequency [52,114].

Consistent with the dentate gyrus performing a pattern separation function (Box 2: CA3 collaterals and the dentate gyrus) for spatial information, several studies implicate the dentate gyrus in spatial-novelty-elicited rearing, for example following changes to environmental geometry (Figure 2F) [129,134,140–142]. Importantly, when rearing on hind legs is experimentally enhanced and prevented, spatial learning of object locations is also respectively enhanced and prevented [142]. In contrast,

object-identity learning is unaffected by these manipulations, suggesting that rearing may be particularly important for acquiring spatial knowledge [142].

Though suggestive, these rearing studies did not directly investigate the relationship of exploration to cellular spatial mapping. Excitingly, one study [143] of headscans did manage this. In this work, mismatch trials consisted of rotations of extra-track cues with respect to intra-track cues. As expected for a spatially-directed investigative behaviour, the sensory view sampled during a headscan widened in response to greater mismatches of the spatial cues. Importantly, these investigative headscans predicted the appearance, or abrupt strengthening, of CA3 and CA1 place fields in novel and familiar rooms. In summary, during both the construction of novel maps and the updating of existing maps, this exploratory behaviour responded to spatial novelty and initiated place field formation.

Taken together, these rearing and headscanning studies align with a model [11] of how the hippocampal mapping system first detects spatial novelty, then directs effortful, but intrinsically rewarding, exploratory actions aimed at acquiring allothetic spatial knowledge, and then incorporates this exploration-enhanced knowledge into spatial maps, which are subsequently useful. This sketch has emphasised allothetic information, but many mammals make great use of idiothetic cues as well as allothetic cues. How might these two types of spatial information be integrated? For recent neurocognitive-mechanistic reviews of such integration, see [40,144]. In Box 3, we suggest that one major organizing principle of long-duration exploratory behaviour, the 'home base', has evolved to integrate allothetic and idiothetic representations, and thus enable accurate, stable spatial mapping.

Map Retrieval

How do animals re-orient after losing their bearings? Search tasks show that mammals are particularly adept at using the geometry of environmental boundaries [145,146]. In one study [147], rats used the geometric properties of a rectangular box to retrieve hidden food at a corner. Because two corners shared identical geometric properties, for example 'short wall left of long wall', rats searched similarly in both those corners. This search equivalence occurred despite unique multimodal features at each corner, and one long wall of the otherwise-black box being white. Thus, although various sensory features unambiguously predicted the goal location, rats typically ignored these to use a less efficient strategy based solely on geometric properties. With extended training, it was shown that rats could use the non-geometric features to disambiguate geometrically-equivalent places [147].

This initial geometric primacy, replicated across mammalian species, including human children, under many (though not all) conditions [148–150], led to the much-debated 'geometric module' theory [147,151,152]. This hypothesised a reorientation-serving module dedicated to coding solely geometric properties of an environment using global shape parameters [147,152]. Gallistel [152] suggested that this makes sense from an evolutionary standpoint as the macroscopic shape of the navigator's environment rarely changes, while other features such as the colour of surfaces and smells do change, across seasons. When animals are not disoriented, boundary cues, especially those near to the animal, exert less control over orientation. For example, in one study [128], polarising environmental shape cues controlled head direction signals only after disorientation. Taken together, the findings show that the geometry of environmental boundaries is highly influential in re-orienting spatial maps after disorientation, but what are the neural underpinnings of this behaviour?

At a cellular level, the orientation of locational maps is controlled by the head direction system, with locational search then guided by the place-cell or boundary-cell system. Importantly, in many circumstances, the boundary cell system may be sufficient to drive behaviour independently of the 'remapping' place cell system, as the results of [153] suggest. One intriguing possibility is that boundary cells, whose firing is specifically attuned to the geometry of environmental boundaries — while being largely insensitive to features such as surface colour and texture, odour, and distal spatial cues, unlike remapping place cells (Figure 2E) — could contribute to the properties of the system characterised as the 'geometric module', as originally envisaged by Cheng and Gallistel [147,152].

Testing the influence of environmental geometry on orientation, Keinath *et al.* [154] recently recorded the firing patterns of place cells, serving as a head-direction-driven orientation correlate. Disoriented mice navigated through an environment in which they could establish heading based on two sources of information: a polarising visual cue and the local geometry provided by the walls of the box (Figure 2G). If place cells were anchored to the polarising cue, providing asymmetry to the navigable search space, then place fields should have occupied a consistent position across trials. However, the results revealed that the position of each cells' place field alternated across trials, confusing geometric-equivalent locations (Figure 2G). Thus, the hippocampal map was anchored to the spatial geometry in spite of a disambiguating polarising cue being available to help establish heading.

A second experiment by Keinath *et al.* [154] investigated whether this map alignment could predict where the navigating mice would search. Although the disoriented mice were continually trained to find food in the corner with a short, striped wall to the left of a long white wall, they first searched both in that corner and its geometric equivalent (Figure 2H left-hand panel): like the hippocampal map, orientation was guided primarily by the geometry of the walls. Moreover, the recovered place-cell representation was highly correlated with the corner in which the mice first searched for food and could reliably predict the to-be-searched corner on each trial. The two right-hand images of Figure 2H show an example cell: when the place field was located close to the north-east corner during trial 1, the mouse first searched for food in the corner containing the black circle; but when the place field was rotated 180° to a geometrically equivalent location in trial 2, the mouse's first search behaviour (black circle) exhibited the same rotational shift. In summary, the geometry of an environment exerts powerful control over reorientation behaviour, likely modulated by the head direction system, with place cells and/or boundary cells guiding search within the map.

Replay

Once maps are retrieved and correctly oriented, the advantages for generating efficient, and potentially novel, routes can be

Box 3. Exploration, map-building and the home base.

The creation of a 'home base' in a novel environment, from which exploratory trips originate, is seen in many mammals including rodents (reviewed in [227]). Over a one hour period in a novel rectangular box in a laboratory, rats spontaneously spend a greatly disproportionate amount of time at one particular location, typically a corner [228]. Reassuringly, lab-based and larger-scale naturalistic findings show good correspondence in terms of journeys from and to the home base: for example, outward paths are slower, more investigatory, while return paths are rapid and direct; and rats show home base behaviour in a large yard [227–230]. The return path typically involves path integration, and hippocampal-lesioned rats are impaired in direct homing even in the light [227,229–231]. This settling upon a single, initially novel, location in the lab likely usefully models not just creating the actual home (e.g. for housing progeny), but also how a mammal extends its home range, selecting an increasing number of 'satellite' home bases in a privileged 'one-at-a-time' manner.

Is there a function of the home base beyond security? As suggested by behavioural studies [227,229,231,232], we propose that home-base creation reflects an exploratory map-building strategy optimising the integration and tuning of allothetic and idiothetic spatial representation, in which the home base functions as a single privileged hub of spatial certainty for error-correction and recalibration of path integration mechanisms, from which spatial knowledge can extend outwards. Arguably, an overlooked observation of rodent home base behaviour in the laboratory is that, beyond the obvious superiority of corners (two boundaries) over sides (single boundaries) over central portions in terms of providing landmarks and protection, selection of the home base location is *arbitrary*. Because box corners are similar, as demonstrated by different animals selecting different corners, why does a given animal spend a greatly disproportionate time at just one place? We suggest home base behaviour is designed to minimise two problems that spatial mapping poses: path integration error, and same-place recognition.

We suggest that home base behaviour reflects the need not only to reset the path integrator, but also to recalibrate its underlying mechanisms. Applied to later development, this argument is admittedly speculative, since it might be assumed that such recalibration is unnecessary, as consistent with the emphasis upon context-invariant rate-to-speed slopes in speed cells in [49]. Certainly, frequent resetting of preferred angle in head direction cells at a lab-defined 'home base' after even short excursions has already been elegantly shown in a homing task [233]. It is possible that linear resetting and recalibration of angular and linear path integrative mechanisms occur also. Recalibration as understood here includes not only altering the weights of the individual sensory contributions to estimates of displacement, but also changing the gain relationships. For instance, if home base arrival is sooner than expected, then the gain of a function relating neural activity to travelling speed (running, flying) may need to be decreased. Using idiothetic information is difficult; errors can arise from several different sensory modalities subserving ideothesis, and from faulty estimates of either/both angular and linear displacement. In summary, pinpointing sources of error is a challenging problem, likely requiring many trials to tune the system optimally.

Circling behaviour ('pivoting') [228] and rearing on hind legs (often involving head rotations) occur at high levels in and around the home base, and enable sensory sampling of external cues from multiple viewpoints. One major goal of this allothetic information-gathering process appears to be to derive a fixed point of spatial stability, aided by distinctive landmark cues at the home base. The concept of spatial stability raises theoretical controversies [11] beyond our scope here, involving the problem of re-identifying 'the same place', given view-limited egocentric sensation, time elapsing between different views, and a changing world. This is related to the 'loop closure' problem in the robotics literature [234]. We suggest that home base behaviour minimises this 'same place' problem by having, initially, just one place to re-identify. Minimising the same-place problem enhances the spatial certainties that aid solving the error-source problem; a repeatedly-visited locus of spatial stability is likely a crucial tool for optimising path integration mechanisms, and combining idiothetic with allothetic cues, beyond just resetting.

In conclusion, home base creation likely reflects not only security-related motivation, but addresses problems associated with spatial map-building. Even if initial inspection suggests several equally-safe locations, it may be adaptive for spatial mapping to establish a privileged hub of spatial certainty, from which spatial knowledge can gradually extend outwards. Exploration is clearly species-dependent and habitat-dependent, but home ranges can be quite extensive [235] even in rodents, averaging, for example, three hectares in Pacific rats in Hawaiian rainforest [236]. Presumably, then, exploration creates 'satellite' home bases, and then integrates mini-maps associated with these nodes of spatial certainty, with mapping gradually extending the size of or developing a new home range.

exploited. Again, it appears that specialized neurobiological mechanisms support this process, and in particular the hippocampus' capacity to 'replay' spatial experience during specific oscillatory states is implicated in both the consolidation of spatial knowledge and in planning future behaviour.

Oscillatory States in the Hippocampus

Various oscillations, including theta (4–12 Hz), gamma (30–150 Hz) and so-called 'ripples' (140–220 Hz), are studied in the context of navigation (see [120,155–157] for recent relevant reviews). Here, we focus on ripples because of their close association with the apparent replay of spatial experience. Although the theta oscillation dominates the hippocampal formation during locomotion in most species, stationary behavioural states are characterised by large irregular activity, within which the transient ~140–220 Hz ripple oscillations are observed, coinciding with large amplitude 'sharp waves' in what is called the sharp wave/ripple complex [11,158]. Ripples also occur during sleep where, as in awake behaviour, they

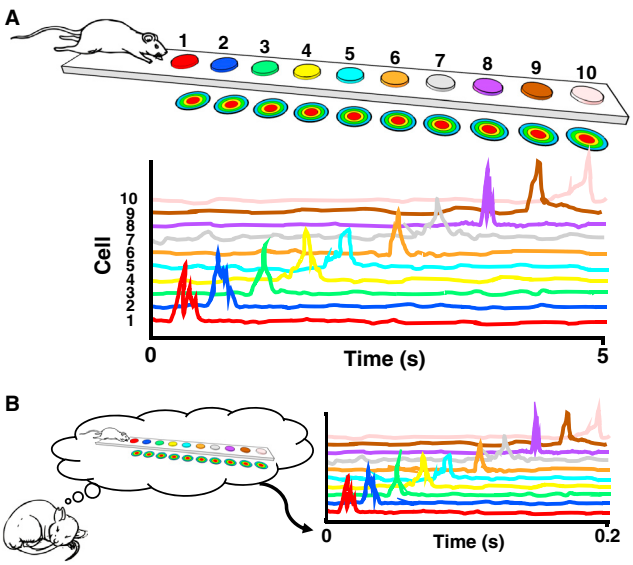

Figure 6. The consolidation of location sequences in replay and theta sequences.

Lee and Wilson [168] suggested how the sequential structure of experience, such as the order of locations experienced when running in one direction on a particular linear track (A, top), represented by cells firing in those locations (A, bottom), could be rehearsed and thus consolidated during slow wave sleep (B). Such a mechanism would suit an episodic memory system in order to learn an event order bound to sequentially-visited locations, such as the smell of food A at place 1, food A itself at place 2, predator odour at place 3, a predator at place 4 and so on. The authors emphasised that experience underwent a ~20-fold compression during this sleep-based replay, leading to intervals between the firing of route-connected cells which suited synaptic learning rules known as 'spike-timing dependent plasticity' (reviewed in [237]). The influential spike-timing dependent plasticity model asserts that pre-before-postsynaptic neuron spiking within a narrow time window (~10–50 ms) elicits long-term potentiation of synapses, while correspondingly post-before-presynaptic spiking elicits long-term depression of synapses [238]. Thus, under a compressed, virtual-route replay regime (B), place cell 1 might fire 20 ms before place cell 2 (signalling an eastwards-visited adjacent location), and place cell 2 might fire 20 ms before place cell 3 (further eastward), potentiating the memory of the eastwards 1-to-2-to-3 route. In contrast, during real locomotion, 400–500 ms might elapse between the place field locations of place 1 and 2, and place 2 and 3 (A, bottom), well beyond the classic spike-timing dependent plasticity window. Thus, importantly, consolidation replay might not only recapitulate experience, but also do so under appropriate synaptic connection-strengthening conditions. The suitability of compressed trajectories to synaptic plasticity is widely agreed. The compression of longer trajectories is not unique to ripple/replay activity, but also occurs during theta states (Figure 3). Theta-state compression may thus also suit spike-timing-dependent plasticity. A potential caveat with learning theta sequences, however, is that they are not very robust on the first lap across a novel track [239], and it is not clear to what extent neuromodulatory influences on plasticity such as widening the spike-timing-dependent plasticity window [130] can mitigate this. In contrast, while there was initial concern that replay required repeated experience [169], which would not suit learning episodic memories, it now seems clear that at least reverse replay can occur subsequent to just one single trial across a novel track [171,174,176]. In summary, consolidation of a route by replaying it backwards (reverse replay) may potentially offer a more robust consolidation mechanism *for novel experiences* than theta sequences.

are mutually exclusive with theta, theta being present during rapid eye-movement (REM) sleep, while ripples occur during slow-wave sleep.

The firing of place cells during ripple events is not random but preserves the spatial relationships between the neurons' place fields, making it possible to construct virtual trajectories while the animal itself is stationary or even sleeping (Figure 6). The cells thus seem to 'replay' spatial experience. Compared to real-world spatial firing patterns, replayed trajectories unfold much more rapidly (over a few tens of milliseconds) and may occur in either forward or reverse directions ('reverse replay'). Studying replay offers potentially fascinating insights into the mechanisms of spatial mapping and navigation (for recent reviews see [159–163]). While replay remains much-debated, these studies arguably suggest that replay serves two functions: to consolidate spatial knowledge ('map building') and to simulate traversable paths ('using maps'). We discuss these functions in turn.

Consolidating Spatial Knowledge

In Marr's influential, systems consolidation model of hippocampal function in episodic memory, information is transferred from the hippocampus to the neocortex during sleep. The idea that ripple activity might represent a Marr-type hippocampus-to-neocortex information transfer phase was proposed in detail by Buzsaki [164]. The suggestion was that theta represents the online learning state, and ripple activity the offline consolidation state. We should emphasise that current concepts of replay as consolidation include replay serving intra-hippocampal as well as hippocampal-neocortical consolidation. As soon as recording technological advances could test these suggestions in slow-wave sleep, they proved prescient in that place cells that fired together during spatial experience preferentially fired together during the sleep following that experience [165,166]. Many subsequent studies continued to suggest a consolidation function for replay during sleep [167,168] and during broadly-stationary waking states [169–173], where reverse replay was strikingly clear [170,171,173].

A success of replay research, exemplified in Lee and Wilson's seminal forward-replay study [168], was identifying a plausible mechanism by which spatial sequences could become amenable to rules governing synaptic plasticity, and thus consolidated into memory (Figure 6). But what exactly is being consolidated in replay? Foster [161] argues, contrary to the replay-as-recapitulation model, that replays may not represent segments of experience but rather "a model of the world" reflecting "which paths are traversable". Studies examining replay in complex environments may help to decide between recapitulation or model-building accounts. In one study [174], the paths leading to a maze's left arm or right arm were always taken from the central arm. Intriguingly, despite this stereotyped path pattern, replay events occurred which represented the 'shortcut' path from the left to right arm, even though this path was never experienced. Such replay appears to embody a Tolman-like 'cognitive map' in which spatial knowledge is inferred from discrete experiences [6]. Other studies also support the model-construction, rather than experience-recapitulation, concept [161–163,175,176].

A minimal prediction from the replay-as-consolidation model is that inhibiting ripples should disrupt the overall process of spatial learning, and evidence supports this prediction [177–179]. For instance, Girardeau *et al.* [177] timed disruptive stimulation to either ripple or non-ripple states during the sleeps following learning of a spatial reference task and found that ripple-stimulated rats consistently performed worse. Though such work has not yet selectively inhibited replay, but rather inhibited ripple states more generally, it suggests that

ripples may contribute to a consolidation-dependent component of learning. In summary, while the contents of consolidation may be debated, the replay-as-consolidation model remains promising.

Consistent with systems-consolidating ripple activity transferring information from the hippocampus to neocortex, hippocampal replay/ripples orchestrate activity in regions downstream of the hippocampus, such as the prefrontal cortex [180] and deep entorhinal cortex [181,182]. Olafsdottir *et al.* [182] showed that replay in the medial entorhinal cortex lagged CA1 place cell replay by ~10 ms, as if hippocampus initiated entorhinal grid replay. These data are clearly consistent with the systems consolidation replay model.

Planning for Elsewhere

If replay was *purely* a systems-consolidation phenomenon, we would always expect to see ripples/replay begin in hippocampus proper (CA3 then CA1) and then propagate to hippocampal output regions. Complicating this picture of hippocampally-led systems consolidation, however, medial entorhinal replay in superficial layers is often independent of CA1 replay [183], while layer 3 medial entorhinal input seems necessary for extended hippocampal replay during quiet waking [184]. These dual-region replay studies, and many others, have thus suggested functions for replay in addition to consolidation, such as planning in navigation tasks [161–163,185].

Perhaps the clearest example of navigational planning was shown in a task involving a goal whose location was stable on any given day, but changed from one day to the next [186]. Strikingly, replay events occurring shortly before goal-directed navigation tended to be forward replays predicting future paths to the current day's goal, including paths not previously taken that day. Furthermore, replays were more predictive of future paths than measures of heading, indicating that replays were not merely prospecting paths directly in front of the rat. Consistent with forward replay of 'routes ahead' at decision points in spatial tasks [187–189], causal evidence links awake replay to navigational planning [190]. When ripple events were truncated by stimulation at decision points in a spatial working memory alternation task, task performance was significantly impaired [190].

What exactly is being planned in replay episodes? Intriguingly, trajectory distance correlates strongly with the total duration of its replay (with concatenated ripple events for long trajectories) [175,176]. Thus, readout of replay duration could help in navigational planning to select shorter paths [161]. In general, replay may be simulating various possible trajectories to enable evaluation of the costs and benefits of particular journeys. This would be consistent with observations where replay and theta sweeps reflect a menu of potential alternatives, rather than simply predict behavioural choices [60,174].

The cost–benefit analysis that replay enables need not be limited to goal-seeking and efficiency savings but could extend to other adaptive behaviours, by using replay simulations to retrieve associations with particular places. So, for instance, after shock training at one end of a track, hippocampal replay events depicting virtual trajectories towards the shock zone were associated with behaviours avoiding that zone [189]. An important challenge is thus to understand how goals [191], obstacles [32,33] and punishments are incorporated into replay to direct future behaviour. For example, it has been speculated that boundary cells' function might extend to reflect aversive, for example social or predator-related, barriers to movement [192]. Incorporating boundary cells into hippocampal replay studies might be fruitful. Overall, studies of replay indicate that the hippocampal formation does not merely reflect ongoing spatial behaviour, but serves offline consolidation and planning.

While navigation tasks vary widely, a typical contribution of the hippocampal formation will be to calculate a vector or path to a distal/hidden goal [11,193,194] (for reviews see [132,195,196]), likely involving theta sequences and/or replay. From a computational perspective, grid cells may be particularly helpful for vector-based navigation, for example in planning direct routes cutting across unvisited areas or taking shortcuts, and several theoretical models have outlined how grid cells can be used to compute vectors from a starting to goal location over large-scale space [193,195–199]. A general advantage of using grid cells over place cells is that, at least after sufficient exploration [200], universal coordinate frames, at different scales corresponding to different grid modules, become available. The ability to combine activity from different grid modules enables calculation of start-to-goal vectors whose length exceeds that of the largest grid scale. In contrast, place-cell firing can only indicate local relationships within an environment and, because of hippocampal remapping, relationships between place cells in different environments are often arbitrary.

These grid cell vector navigation models can be divided into decoding models and 'look ahead' models (see discussion in [196]). Decoding models have the advantage of being able to compute translation vectors quickly, but postulate additional neural mechanisms yet to be identified, such as distance cells [196,198] or grid cells exhibiting phase precession aligned with specific one-dimensional axes, as in the phase-coded vector cell model [196]. Look-ahead models [193,195,196] have the advantage of making use of already-identified neural mechanisms, but have the limitation that calculation duration correlates with distance, which could be burdensome for long distances [196]. While grid cells offer computational advantages, it remains unclear how grid cell networks can be interrogated: replay is a good candidate, but goal-directed grid replay remains to be shown.

Once vectors are calculated, other regions aside from the hippocampus might play a more active, moment-to-moment role in guiding ongoing travel [201,202]. This would be consistent with hippocampal formation population activity peaking towards journey beginnings, and such activity predicting navigational accuracy [194,203–206].

Conclusions

Navigation in mammals makes use of a dedicated system that exploits latent learning, together with specific, purposeful exploratory behaviours to build up cognitive maps of the environment, based on specialised spatial cells in the hippocampal formation and its inputs. Studies in rodents show that navigation to hidden goal locations can draw on a wide variety of external and internal sources of information about location, orientation and movement. Allothetic information related to distal visual cues and environmental geometry (coded by boundary cells) is particularly important in establishing orientation (coded by the head direction system) and

location (coded by hippocampal place cells and medial entorhinal grid cells), but idiothetic information appears to play a vital role in tracking movement (perhaps with respect to time and speed cells) and in stabilizing and extending the representation of location into open spaces. In turn, cellular codes for idiothetic information, in particular, appear to be linked to theta oscillations that dominate the network during locomotion and are modulated by speed.

When an animal is stationary, access to the map is reflected in distinct oscillatory states in the hippocampus which are associated with consolidation of existing spatial knowledge and with navigational planning. These plans include generating direct routes to goals, negotiating obstacles, and avoiding punishing places. Many facets of these cognitive processes remain obscure, but the close connection between ongoing spatial behaviour and neural activity within the hippocampal formation, coupled with emerging clarity over the role of offline mechanisms such as replay, provide unique tools for discovery.

This review has emphasised apparently common mammalian characteristics. However, many questions remain about the extent to which the neural mechanisms that support spatial representation are specialized (neurons, oscillations, regions) according to the sensory and behavioural adaptations of different species — for example, echolocation, gaze, flight, swimming, burrowing — especially in large-scale two-dimensional and three-dimensional space (sky, sea). For instance, while oscillations apparently play a major role in hippocampal formation function in rodents — in path integration, scheduling encoding versus retrieval, consolidation and planning — translating insights from rodents to bats, primates, and sea mammals may not be straightforward. Other open questions concern the way the hippocampal formation interacts with other systems, for instance in optimizing exploration vs exploitation, perceiving and recognizing places, generating spatial imagery, and forming episodic-like memories. Answering these questions, to obtain an integrated view of the uses of cognitive mapping within and beyond navigation, may require high-density recording technologies whose multi-region coverage can approach whole-brain technologies like fMRI.

ACKNOWLEDGEMENTS

This work was supported by a BBSRC research grant to C.L. (BB/M008975/1). We thank Neil Burgess, Francesca Cacucci, Sang Ah Lee, and Thomas Wills for discussion. We would like to acknowledge the contribution of our anonymous reviewers to improving our manuscript, and apologise to colleagues whose work we have been unable to cite due to space restrictions.

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